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Silvia Novello, MD, PhD, Giorgio Scagliotti, MD, PhD, Gilberto de Castro, Jr., MD, PhD, Murat Kiyik, MD, Rubén Kowalyszyn, MD, MC, Karl-Matthias Deppermann, MD, Edurne Arriola, MD, PhD, Lionel Bosquee, MD, Ruslan D. Novosiadly, MD, PhD, Tuan S. Nguyen, PhD, Amelie Forest, MSc, Shande Tang, PhD, Siva Rama Prasad Kambhampati, PhD, Jan Cosaert, MD, Martin Reck, MD, PhD

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Brief Report

Brief Report: An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as a First-Line Therapy in Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer

Silvia Novello, MD, PhD,^{*} Giorgio Scagliotti, MD, PhD,^{*} Gilberto de Castro, Jr., MD, PhD,[†] Murat Kiyik, MD,[‡] Rubén Kowalyszyn, MD, MC,[§] Karl-Matthias Deppermann, MD,^{||} Edurne Arriola, MD, PhD,[¶] Lionel Bosquee, MD,[#] Ruslan D. Novosiadly, MD, PhD,^{**} Tuan S. Nguyen, PhD,^{††} Amelie Forest, MSc,^{**} Shande Tang, PhD,^{‡‡} Siva Rama Prasad Kambhampati, PhD,^{§§} Jan Cosaert, MD,^{||¶¶} Martin Reck, MD, PhD^{##}

^{*}Department of Oncology, University of Turin, S. Luigi Hospital, Torino, Italy; [†]Clinical Oncology Service, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [‡]Pulmonary Department, Yedikule Chest Disease Hospital, Istanbul, Turkey; [§]Centros de Investigaciones Clinicas, Clinica Viedma, S. A. Rio Negro, Argentina; ^{||}Lungenzentrum - Klinik für Pneumologie, Sana Kliniken Düsseldorf, Düsseldorf, Germany; [¶]Servei d'Oncologia Medica, Hospital del Mar, Barcelona, Spain; [#]Centre Hospitalier de Bois de L-Abbaye, Seraing, Belgium; ^{**}Department of Cancer Immunobiology, Eli Lilly and Company, New York, NY, USA; ^{††}Statistics-Oncology Department, Eli Lilly and Company, Indianapolis, IN, USA; ^{‡‡}Statistics-Oncology Department, Eli Lilly and Company, Bridgewater, NJ, USA; ^{§§}Global PK/PD & Pharmacometrics, Eli Lilly and Company, Bridgewater, NJ, USA; ^{¶¶}Clinical Sciences, Early Phase, Eli Lilly and Company, Bridgewater, NJ, USA; ^{##}Department of Thoracic Oncology, LungenClinic Grosshansdorf, Airway Research Center North (ARCN) Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany

^{¶¶}Current affiliation: SOTIO a.s, Prague, Czech Republic

Corresponding Author

Dr. Silvia Novello, MD, PhD

Department of Oncology, University of Turin, S. Luigi Hospital, Torino, Italy

Phone: 39 011 9015184

Fax: 39 011 9026.414

Email: silvia.novello@unito.it

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G. Scagliotti has received honoraria from AstraZeneca, Eli Lilly and Company, Roche, and Pfizer. G. Castro is an advisory board member for MSD and Novartis. G. Castro has also received honoraria for lectures from Eli Lilly, MSD, AstraZeneca, and Roche. K-M.

Deppermann is an advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, and Hoffmann La Roche and has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, BMS, and Novartis. R. Novosiadly, T.S. Nguyen, A. Forest, S. Tang, and S.R.P. Kambhampai are employees of Eli Lilly and Company (J. Cosaert was an employee of Eli Lilly and Company at the time of the study). M. Reck is an advisory board member for Hoffmann La Roche, Eli Lilly and Company, Pfizer, Bristol-Myers Squibb, AstraZeneca, and Daiichi-Sankyo. M. Reck has also received honoraria for lectures from Hoffmann La Roche, Eli Lilly and Company, Pfizer, Bristol-Myers Squibb, AstraZeneca, and Daiichi-Sankyo. All other authors do not have any financial relationships to disclose.

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Abstract

Introduction: Type 1 insulin-like growth factor receptor (IGF-IR) is deregulated in solid tumors. Cixutumumab, a monoclonal antibody that inhibits IGF-IR activity, was investigated in combination with pemetrexed/cisplatin in the front-line setting.

Methods: In this open-label, Phase II study, patients with Stage IV nonsquamous non-small cell lung cancer (NSq-NSCLC) and a performance status of 0–1 were randomized (1:1) to receive 20 mg/kg cixutumumab, 500 mg/m² pemetrexed, and 75 mg/m² cisplatin (cixutumumab; *n* = 87) or pemetrexed and cisplatin (control; *n* = 85). Eligible patients received pemetrexed-based maintenance therapy with (cixutumumab arm) or without (control arm) cixutumumab. The primary endpoint was progression-free survival (PFS). Secondary endpoints assessed overall survival (OS), objective response rate (ORR), and safety. Survival was analyzed by Kaplan-Meier method and Cox's proportional hazard model. Exploratory correlative analyses were also performed.

Results: The mean age of the intent-to-treat (ITT) population (*n* = 172) was 59 years (range, 32–83). Median PFS was 5.45 months with cixutumumab vs. 5.22 months with control (hazard ratio [HR] 1.15; 95% confidence interval [CI], 0.81–1.61; *P* = 0.44). Median OS was 11.33 months with cixutumumab vs. 10.38 months with control (HR 0.93, 95% CI, 0.64–1.36). ORR did not differ between treatments (*P* = 0.338). Grade 3/4 hyperglycemia occurred at a higher rate with cixutumumab than control (9.4% vs. 1.2%). One death possibly related to cixutumumab occurred.

Conclusions: Efficacy was not improved in NSq-NSCLC patients when cixutumumab was added to pemetrexed/cisplatin. Combination therapy was well tolerated and no new safety concerns were reported.

Keywords: cixutumumab, IMC-A12, first-line therapy, pemetrexed, NSCLC

INTRODUCTION

Nonsquamous non-small cell lung cancer (NSq-NSCLC) accounts for the majority of patients with NSCLC and often presents as advanced/metastatic disease at diagnosis. On average, the median survival time of untreated patients with advanced NSq-NSCLC is approximately 4 months after diagnosis. However, for patients with good performance status, first-line platinum-based chemotherapy improves both survival and quality of life.¹

Platinum-based doublets have shown no significant differences in objective response rate (ORR), progression-free survival (PFS), or overall survival (OS).^{2,3} Other clinical factors not considered with traditional chemotherapy, such as histologic subtype, may also influence clinical outcome. Patients with advanced NSCLC with non-squamous histology benefited more from pemetrexed/cisplatin than cisplatin/gemcitabine in terms of OS (hazard ratio [HR] 0.81; $P = 0.005$), while PFS was similar between arms.⁴ This evidence provided a rationale for the current patient population in addition to the need for effective treatments for patients with NSq-NSCLC who may not have oncogenic alterations.

It is clear that type 1 insulin-like growth factor receptor (IGF-IR) has significant implications in NSCLC. Cixutumumab (IMC-A12; Eli Lilly and Company, Indianapolis, IN, USA), a human IgG monoclonal antibody, blocks IGF-IR activity and inhibits tumor survival and growth in numerous solid tumor types, including lung cancer, and in human tumor xenograft models *in vivo*, both alone⁵ and combined with chemotherapy.⁶ However, the clinical benefit of adding cixutumumab to chemotherapy in patients with advanced NSq-NSCLC is unknown.

This open-label, multicenter, randomized Phase II study assessed whether adding cixutumumab to pemetrexed/cisplatin was superior to pemetrexed/cisplatin as first-line therapy

in patients with advanced NSq-NSCLC. Biomarkers potentially predictive of cixutumumab efficacy were also evaluated.

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MATERIALS AND METHODS

Patients and Study Design

An overview of the study design and treatment plan has been fully described in Figure 1. Prior to enrollment, an institutional review board reviewed and approved the study protocol. Patients who met the eligibility criteria (Figure 1) were enrolled in the study. Intravenous (IV) cixutumumab infusions were administered first, followed by an IV pemetrexed infusion 1 hour later and an IV cisplatin infusion 30 minutes after pemetrexed. All patients received vitamin B₁₂, folic acid supplementation, and prophylactic dexamethasone. Patients continued maintenance therapy until disease progression, unacceptable toxicity, noncompliance, or withdrawal of consent.

Statistical Analysis

Patients ($n = 156$) were planned for the superiority test of comparing PFS, assuming a median PFS of 5.3 months (control arm) and an expected median PFS of 7.16 months (cixutumumab arm; HR cixutumumab/control = 0.74). With a power of 80% (1-sided significance level of 20%; 1:1 ratio) to detect an HR of 0.74, 125 events were required for analysis.

The HR of cixutumumab/control for PFS was determined using the Cox's proportional hazard model. PFS, OS, and time-to-progressive disease (TTPD) were estimated using the Kaplan-Meier method and differences assessed by log-rank test. The ORRs were compared using Fisher's exact test. Radiographic imaging assessed the percentage change in tumor size from baseline to the end of cycle 2; comparisons were analyzed using a t-test. Safety was assessed using Common Terminology Criteria for Adverse Events version 4.0.

An exploratory correlative research and a pharmacokinetics (PK) analysis of cixutumumab were also performed (see Supplemental Digital Content text for analysis methods).

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RESULTS

Clinical Efficacy

A total of 172 patients were randomized (cixutumumab, $n = 87$; control, $n = 85$). Patients discontinued in the cixutumumab and control arms, respectively, due to progressive disease (40% and 37%), adverse events (AEs; 20% and 15%), and death (11% for both arms). Baseline patient and disease characteristics (Table 1) of the ITT population were similar between arms.

The median PFS was 5.45 months with cixutumumab and 5.22 months with control (HR 1.15; 95% confidence interval [CI], 0.81–1.61), with no statistically significant difference between arms (Figure 2A). Similarly, no statistically significant difference in OS between arms was observed, but the median OS (Figure 2B) was numerically higher with cixutumumab than control (11.33 months vs. 10.38 months; HR 0.93; 95% CI, 0.64–1.36).

The ORR was 37.9% and 30.6% with cixutumumab and control, respectively ($P = 0.338$). Best tumor responses were similar between arms (Table 2), with more patients experiencing a partial response (37.9% vs. 30.6%) or progressive disease (16.1% vs. 12.9%) with cixutumumab than control. There was a similar percentage of clinical benefit responders between arms ($P = 0.511$).

The median TTPD was 6.05 months with both cixutumumab (95% CI, 5.32–7.79) and control (95% CI, 4.93–7.89). In addition, although the mean percent change from baseline in tumor size was greater with cixutumumab (mean \pm standard deviation, -23.88 ± 18.86) versus control (-16.04 ± 26.14), the difference was not statistically significant.

Safety

The safety analyses included 166 patients (cixutumumab, $n = 85$; control, $n = 81$). As shown in Table 3, Grade 3 or 4 treatment-emergent AEs possibly related to treatment occurred more frequently with cixutumumab (56.5%) than control (43.2%). As expected, hyperglycemia (all grades) occurred at a higher rate with cixutumumab (41.2%) than control (7.4%). Dehydration (all grades), a known effect of cisplatin treatment, was also more frequently reported with cixutumumab (17.7%) than control (6.2%).

Discontinuation rates due to serious AEs (SAEs) possibly related to any study drug were similar between arms (cixutumumab, 7.1%; control, 8.6%). Three patients experienced SAEs possibly related to cixutumumab that led to discontinuation (1 SAE each of myocardial infarction, pancytopenia, and sepsis). Four patients in each arm died and deaths were considered possibly related to any study drug; 1 death (due to sepsis) was possibly cixutumumab related.

Pharmacokinetics

PK analysis of cixutumumab was performed using available serum concentration-time data ($n = 83$; Supplemental text). Overall, serum concentrations of cixutumumab increased after each cixutumumab infusion and accumulation of cixutumumab was observed (Supplemental Figure 1). Cixutumumab clearance was low (0.02 L/hr) and had a long terminal elimination half-life (8 days; Supplemental Table 1).

Exploratory Correlative Analyses

Circulating and tumor-specific candidate biomarkers were also evaluated (Supplemental text and Supplemental Tables 2-5). No statistically significant interactions were demonstrated; however, compared with the control arm, numerically longer PFS, OS, or both PFS and OS were

observed in cixutumumab-treated patients with low circulating total IGF-I levels (25th percentile cutpoint), *TP53* mutations, and high IGF-IR/IR ratio (75th percentile cutpoint) in tumor tissue, respectively.

DISCUSSION

This phase II study failed to support the hypothesis that adding cixutumumab to pemetrexed/cisplatin was superior to pemetrexed/cisplatin alone as first-line therapy in patients with advanced, metastatic NSq-NSCLC. No new safety concerns were reported. Similarly, studies of cixutumumab combined with other chemotherapies as a first-line therapy in other solid tumors have also found little to no benefit from adding cixutumumab.^{7,8}

The lack of efficacy observed may be due, at least in part, to the administration sequence of IGF-IR inhibitors and chemotherapeutic agents.⁹ In breast cancer cells, growth inhibition improves when chemotherapy (doxorubicin and gemcitabine) is administered before IGF-IR inhibition, and an opposite effect with the reverse administration.^{10,11} Here, cixutumumab was administered first followed by pemetrexed/cisplatin, all on the same day.

The addition of cixutumumab to pemetrexed/cisplatin chemotherapy did not lead to any significant increase in toxicity, except for hyperglycemia, which is common among cixutumumab patients. Similar safety profiles have been observed when cixutumumab was combined with mitotane⁷ and gemcitabine and erlotinib.¹² Dose-limiting toxicities were reported when erlotinib and cixutumumab were combined in patients with NSCLC, a finding supported when other anti-IGF-IR monoclonal antibodies were unsuccessfully combined with full-dose erlotinib in patients with NSCLC.⁸

Clinical biomarkers may also predict clinical outcomes for IGF-IR-directed therapy. Since IGF-IR monoclonal antibodies failed to demonstrate significant clinical benefit in general patient populations,¹³ studies are exploring the relationship between circulating biomarkers and clinical outcome. Elevated IGF binding protein-1 correlated with improved PFS ($P = 0.009$) and OS ($P = 0.003$) in patients with advanced hepatocellular carcinoma who were administered

cixutumumab.¹⁴ In addition, low IGF-I baseline levels were associated with significantly shorter OS with a figitumumab combination therapy regimen versus control ($P = 0.01$), whereas patients with high HbA1c baseline levels had a lower median OS with combined figitumumab therapy versus control ($P = 0.05$).¹⁵ Based on our exploratory biomarker analysis, numerically longer PFS, OS, or both PFS and OS were recorded in cixutumumab-treated patients with low circulating total IGF-I levels, *TP53* mutations, and high tumor IGF-IR/IR ratio, respectively. Of note, the biomarker analysis was limited due to the small sample size in subgroups that were defined by marker class by treatment and a high censoring rate in OS.

In summary, cixutumumab added to pemetrexed/cisplatin does not improve clinical outcome as measured in PFS in patients with NSq-NSCLC as a first-line therapy. Our findings corroborate the work of others and suggest that IGF-IR inhibition is largely ineffective in NSq-NSCLC patients. However, since none of the IGF-IR clinical studies enriched for a specific biomarker population, it is plausible that only select NSq-NSCLC patients benefit from the anti-IGF-IR antibodies. Predictive potential of the IGF-IR/IR ratio, *TP53* mutational status, and total IGF-I levels warrants further investigation in clinical trials with biomarker-driven design.

Figure Legends

Figure 1. Study Design. ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; IGF-IR, type 1 insulin-like growth factor receptor; NSq-NSCLC, nonsquamous non-small cell lung cancer.

Figure 2. (A) Progression-free and (B) overall survival Kaplan-Meier curves for the cixutumumab (red) and control (blue) treatment arms in the ITT population. HR, hazard ratio; CI, confidence interval.

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Table 1. Patient Demographics and Disease Characteristics at Baseline (Intent-to-Treat Population)

	Cixutumumab Arm (<i>n</i> = 87)	Control Arm (<i>n</i> = 85)
Sex, <i>n</i> (%)		
Male	54 (62.1)	53 (62.4)
Race, <i>n</i> (%)		
White	81 (97.6)	80 (96.4)
Non-White	2 (2.4)	3 (3.6)
Missing	4 (4.6)	2 (2.4)
Age (years)		
Mean (SD)	59.5 (9.87)	59.3 (9.96)
Median	59	60
ECOG Performance Status, <i>n</i> (%)		
0	41 (47.1)	41 (48.2)
1	46 (52.9)	44 (51.8)
Basis for Pathological Diagnosis, <i>n</i> (%)		
Histological	74 (85.1)	74 (87.1)
Cytological	13 (14.9)	11 (12.9)
Histology at Entry or Initial Diagnosis, <i>n</i> (%)		
Adenocarcinoma	80 (92.0)	75 (88.2)
Large Cell	1 (1.1)	0
Other	6 (6.9)	10 (11.8)
Disease Stage at Initial Diagnosis, <i>n</i> (%)		
IA/IB	2 (2.2)	0

	Cixutumumab Arm (<i>n</i> = 87)	Control Arm (<i>n</i> = 85)
IIIA	5 (5.7)	6 (7.1)
IIIB	2 (2.3)	1 (1.2)
IV	78 (89.7)	78 (91.8)
Smoking Status, <i>n</i> (%)		
Never	15 (17.2)	13 (15.3)
Ever	72 (82.8)	72 (84.7)
Prior Therapies*, <i>n</i> (%)		
Surgery	13 (14.9)	14 (16.5)
Radiotherapy	17 (19.5)	22 (25.9)
Systemic therapy	3 (3.4)	7 (8.2)

ECOG, Eastern Cooperative Oncology Group; *n*, number of patients; SD, standard deviation.

*Patients may have received more than 1 prior therapy.

Table 2. Best Overall Tumor Response

	Cixutumumab Arm (<i>n</i> = 87)	Control Arm (<i>n</i> = 85)	<i>P</i> value (Fisher's exact test)
Complete response, <i>n</i>	0	0	
Partial response, <i>n</i>	33	26	
% (95% CI)	37.9 (27.7, 48.1)	30.6 (20.8, 40.4)	
Stable disease, <i>n</i>	25	35	
% (95% CI)	28.7 (19.2, 38.2)	41.2 (30.7, 51.6)	
Progressive disease, <i>n</i>	14	11	
% (95% CI)	16.1 (8.4, 23.8)	12.9 (5.8, 20.1)	
Not assessed, <i>n</i> (%)	15 (17.2)	13 (15.3)	
Overall response rate			
CR+PR responders, <i>n</i>	33	26	0.338
% (95% CI, Exact method)	37.9 (27.7, 49.0)	30.6 (21.0, 41.5)	
Disease control rate			
CR+PR+SD responders, <i>n</i>	58	61	0.511
% (95% CI, Exact method)	66.7 (55.7, 76.4)	71.8 (61.0, 81.0)	

CI, confidence interval; CR+PR, complete response and partial response; CR+PR+SD, complete response, partial response, and stable disease; *n*, number of patients.

Table 3. Treatment-Emergent AEs Possibly Related to Any Treatment Reported in $\geq 10\%$ of Patients (Safety Population)

	Cixutumumab Arm (n = 85)				Control Arm (n = 81)			
		Grade				Grade		
CTCAE Term	All Grades	3	4	5	All Grades	3	4	5
Patients with ≥ 1 TEAE	82 (96.5)	39 (45.9)	9 (10.6)	4 (4.7)	72 (88.9)	30 (37.0)	5 (6.2)	4 (4.9)
Anemia	24 (28.2)	8 (9.4)	0	0	28 (34.6)	8 (9.9)	2 (2.5)	0
Anorexia	23 (27.1)	6 (7.1)	0	0	22 (27.2)	1 (1.2)	0	0
Constipation	14 (16.5)	1 (1.2)	0	0	11 (13.6)	0	0	0
Creatinine increased	8 (9.4)	1 (1.2)	0	0	13 (16.0)	1 (1.2)	0	0
Dehydration	15 (17.7)	4 (4.7)	1 (1.2)	0	5 (6.2)	0	0	0
Diarrhea	15 (17.7)	2 (2.4)	0	0	12 (14.8)	2 (2.5)	0	0
Fatigue	33 (38.8)	7 (8.2)	0	0	33 (40.7)	8 (9.9)	0	0
Hyperglycemia	35 (41.2)	7 (8.2)	1 (1.2)	0	6 (7.4)	1 (1.2)	0	0
Mucositis oral	22 (25.9)	3 (3.5)	0	0	10 (12.3)	2 (2.5)	0	0
Nausea	18 (21.2)	4 (4.7)	0	0	25 (30.9)	1 (1.2)	0	0
Neutrophil count decreased	25 (29.4)	12 (14.1)	2 (2.4)	2 (2.4)	21 (25.9)	10 (12.3)	3 (3.7)	1 (1.2)
Platelet count decreased	15 (17.6)	4 (4.7)	3 (3.5)	1 (1.2)	9 (11.1)	1 (1.2)	2 (2.5)	0
Vomiting	30 (35.3)	7 (8.2)	0	0	24 (29.6)	1 (1.2)	0	0
Weight loss	10 (11.8)	0	0	0	7 (8.6)	1 (1.2)	0	0

White blood cell decreased	11 (12.9)	0	4 (4.7)	0	7 (8.6)	1 (1.2)	1 (1.2)	0
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CTCAE, Common Terminology Criteria for Adverse Events; *n*, number of patients; TEAE, treatment-emergent adverse event.
Data are reported as *n* (%) for the highest grade TEAE per patient.

Figure 1. Study Design

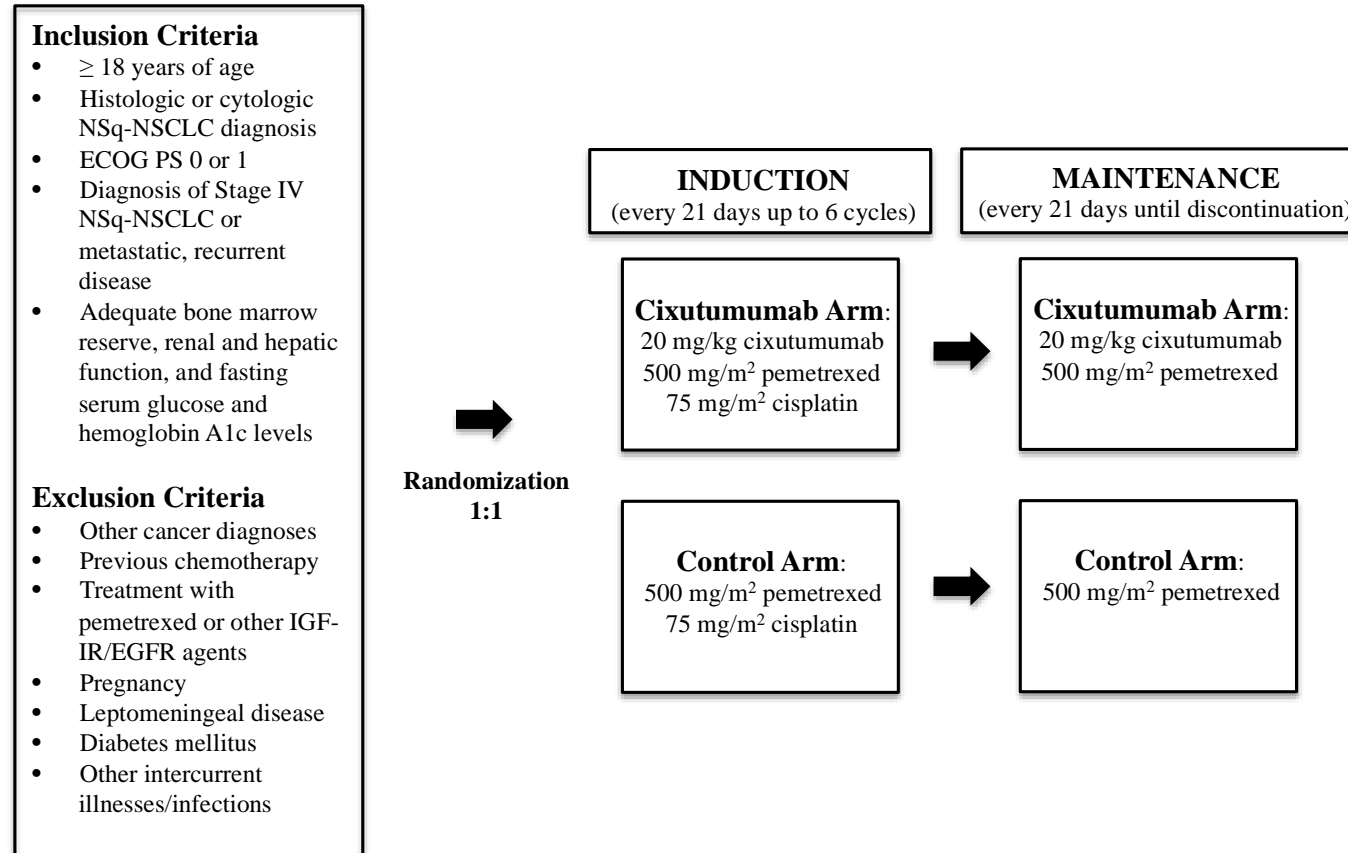


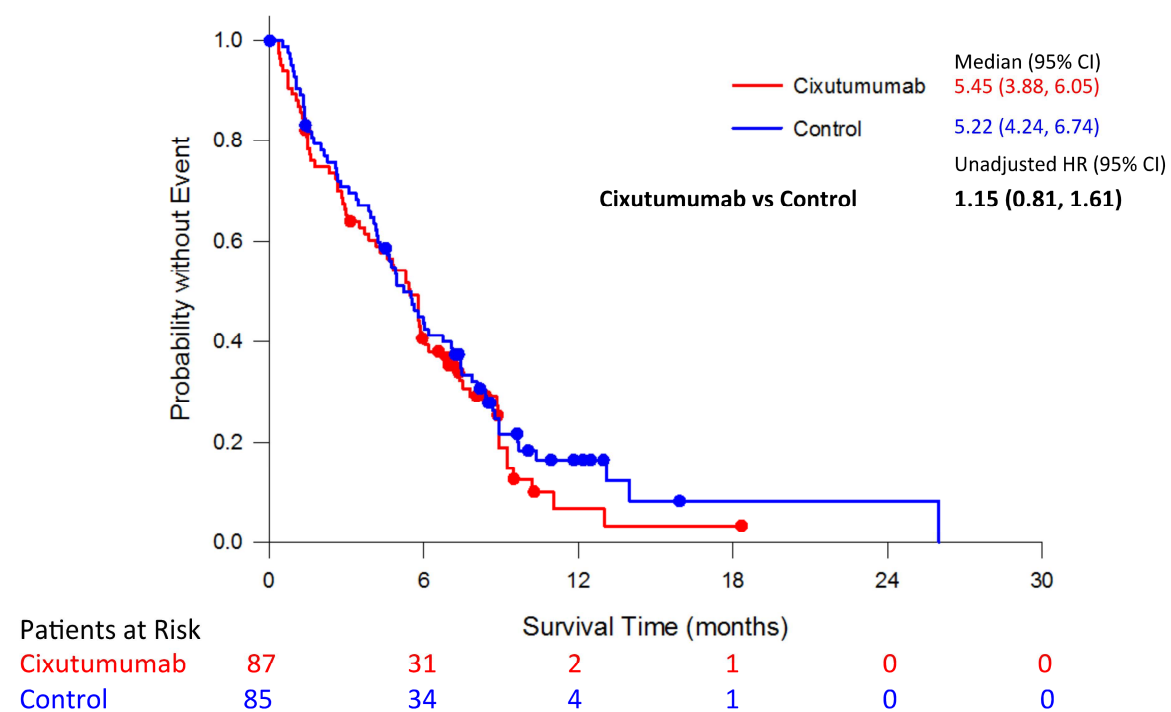
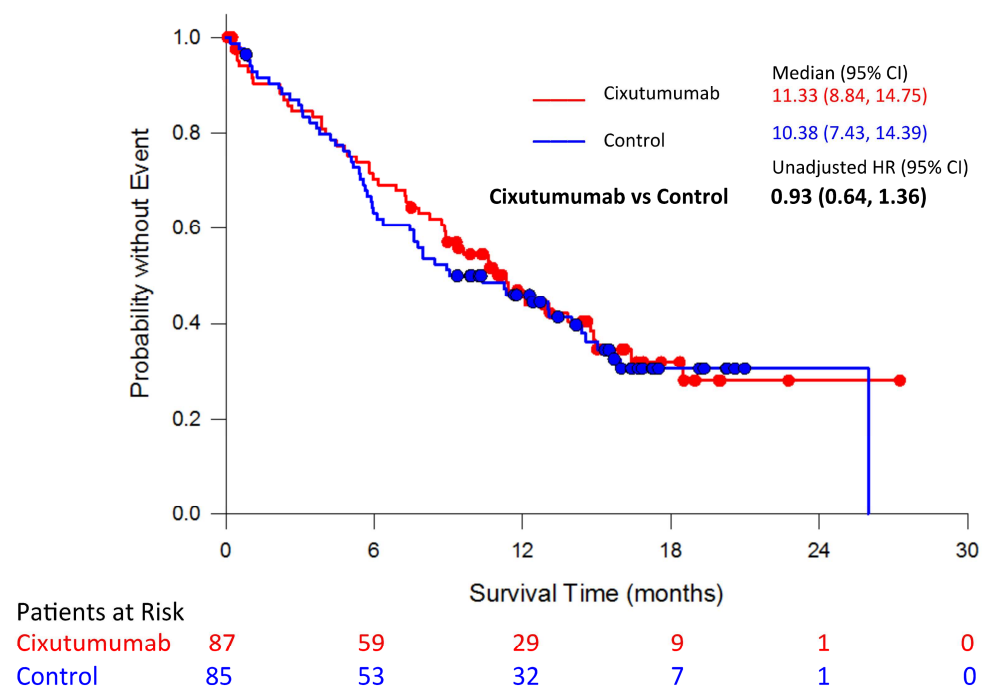
Figure 2A. Progression-Free Survival

Figure 2B. Overall Survival

Supplemental Digital Content

Pharmacokinetic Analysis Methods

Cixutumumab serum concentration in pharmacokinetic (PK) samples was determined using a validated enzyme-linked immunosorbent assay (ELISA) method at Pharmaceutical Product Development (PPD; Richmond, VA, USA). The lower limit of quantification was 2500 ng/mL, and the upper limit of quantification (ULOQ) was 100 000 ng/mL. Samples with values above the ULOQ were diluted to yield results within the calibrated range. The inter-assay accuracy (% relative error) during validation ranged from -7.93% to 3.14%. The inter-assay precision (% relative standard deviation) during validation ranged from 8.70% to 23.0%.

Serial blood samples for PK analysis were collected approximately at pre-dose and at 1, 168, 336, and 504 (also referred to as pre-infusion sample for subsequent cycle) hours post end of infusion following first through fourth infusions. Additional samples were collected approximately 72 hours post end of the first infusion; and at approximately 24, 72, 120, and 240 hours post end of the fourth infusion. From the eighth infusion onwards, 2 samples (pre- and 1 hour post end of infusion) were collected at every fourth infusion.

PK data were analyzed by non-compartmental analysis using Phoenix WinNonlin (Version 6.3).

Pharmacokinetic Analysis

PK analysis was performed using available serum concentration-time data (n = 83). Serum concentrations of cixutumumab increased between the first through fourth

infusions and showed accumulation of cixutumumab when administered every 3 weeks (Supplemental Figure 1) and geometric mean accumulation ratio calculated using AUC was 1.18 (coefficient of variation [CV%], 33%). The geometric means of cixutumumab concentrations before the eighth and twelfth infusions were 65.9 $\mu\text{g/mL}$ (CV%, 70%; $n = 17$) and 94.6 $\mu\text{g/mL}$ (CV%, 57%; $n = 8$), respectively. Cixutumumab has low clearance (0.02 L/hr) and long terminal elimination half-life (8 days; Supplemental Table 1).

Exploratory Correlative Research Methods

Sample collection was mandatory for these analyses. Pretreatment serum or plasma samples were collected to assess circulating levels of insulin, C-peptide, free IGF-I, total IGF-I, total IGF-II, IGF binding proteins 1-3 (IGFBP-1, IGFBP-2, IGFBP-3) by enzyme-linked immunoassay (ELISA; LabCorp, New York, NY, USA). Pretreatment formalin-fixed paraffin-embedded tissue samples were subjected to total RNA and genomic DNA extraction followed by evaluation of type 1 insulin-like growth factor receptor (IGF-IR), insulin receptor A and B isoforms (IRA, IRB), ratio of IGF-IR to total IR, IGF-I, IGF-II, IGFBP-3, INSIG2, ERCC1, TYMS, IL10, and ITGB3 mRNA expression (Asuragen, Austin, TX, USA) and mutational analysis of *TP53* (exons 4-9) and *KRAS* (exon 2) genes using TaqMan qPCR and the SURVEYOR-WAVE Nucleic Acid High Sensitivity Fragment Analysis System (Transgenomic, New Haven, CT, USA), respectively. All assays were analytically validated and were fit for the intended use. The list of TaqMan[®] gene expression assays (Life Technologies, Grand Island, NY, USA) is provided below (Supplemental Table 2).

Each marker was independently analyzed against efficacy endpoints (progression-free survival (PFS) and overall survival (OS) using a treatment-dependent interaction model. Patients were dichotomized into high- and low-expression subgroups using the 25th, median, and 75th percentile cutpoints for continuous biomarkers (circulating proteins and mRNA-based biomarkers), and into mutation positive and negative (wildtype [WT]) subgroups for *TP53* and *KRAS* mutations. Cox regression interaction model included dichotomized marker expression class, treatment indicator, interaction between marker class and treatment, and additional baseline covariates (age group [<65 vs. ≥ 65], gender

[female vs. male], and smoking status [ever vs. never]). All translational research analyses were exploratory and conducted at a 2-sided alpha level of 0.05. No multiplicity adjustments were performed across markers and endpoints.

Exploratory Correlative Research

Of the 172 patients in the intent-to-treat (ITT) population, biomarker analyses included 142 (82.6%), 122 (70.9%), and 126 (73.3%) patients with at least 1 evaluable assay for immunoassay, gene expression, and mutational analysis data, respectively. Baseline demographics were similar between the ITT and biomarker populations; however, minor differences in PFS and OS were noted between the ITT populations and biomarker populations (data not shown).

Circulating Biomarkers

Significant interaction effects between dichotomized protein levels and treatment were observed for serum total IGF-I and PFS (25th percentile Q1 cutpoint), and plasma IGFBP-3 and OS (75th percentile Q3 cutpoint). Patients with low total IGF-I (Q1 cutpoint = 103 ug/L) generally had longer PFS in the cixutumumab arm (PFS hazard ratio [HR] [95% CI], 0.60 [0.28-1.31], $P = 0.204$, interaction $P = 0.027$), while patients with high total IGF-I generally had longer PFS and OS in the control arm (PFS HR [95% CI], 1.72 [1.07–2.77], $P = 0.023$, interaction $P = 0.027$; OS HR [95% CI], 1.37 [0.70–2.67], $P = 0.354$, interaction $P = 0.240$). Patients with high IGFBP-3 expression (Q3 cutpoint = 142.598 nmol/L) had generally longer PFS and OS in the control arm (PFS HR [95% CI], 2.13 [0.94–4.81], $P = 0.073$, interaction $P = 0.170$; OS HR [95% CI], 3.07 [0.92–10.25],

$P = 0.057$, interaction $P = 0.045$; Supplemental Table 3). No significant interaction effects were observed for other circulating proteins and PFS and OS.

mRNA-based Biomarkers

No significant interaction effects were observed for dichotomized mRNA-based biomarkers and PFS and OS. Although not significant, patients with high IGF-IR/IR ratio (Q3 cutpoint = 2.49) generally had longer PFS and OS in the cixutumumab arm (PFS HR [95% CI], 0.61 [0.26–1.43], $P = 0.249$, interaction $P = 0.057$; OS HR [95% CI], 0.46 [0.14–1.53], $P = 0.189$, interaction $P = 0.193$), while patients with lower ratio generally had longer PFS in the control arm (PFS HR [95% CI], 1.57 [0.95–2.61], $P = 0.076$, interaction $P = 0.057$; Supplemental Table 4).

TP53 and KRAS Mutations

No significant interaction between *TP53* and *KRAS* mutations and PFS or OS was observed. Patients with somatic *TP53* mutations generally had longer OS in the cixutumumab arm (OS HR [95% CI], 0.68 [0.35–1.32], $P = 0.255$, interaction $P = 0.067$), while patients that were WT *TP53* had longer PFS and OS in the control arm (PFS HR [95% CI], 2.11 [1.11–4.02], $P = 0.020$, interaction $P = 0.056$; OS HR [95% CI], 1.79 [0.80–4.02], $P = 0.146$, interaction $P = 0.067$; Supplemental Table 5). No apparent association between *KRAS* mutations and cixutumumab efficacy was observed.

Supplemental Table 1. Summary of Pharmacokinetic Parameters of Cixutumumab Following Every 3 Weeks of Cixutumumab Infusions^a With Cisplatin and Pemetrexed as First-Line Therapy in Patients With Advanced Nonsquamous NSCLC

Infusion Number	PK Summary	C _{max} ^b (μg/mL)	t _{max} ^c (hr)	t _{1/2} ^d (days)	AUC ^e (μg*hr/mL)	CL ^f (L/hr)	V _{ss} (L)
First	n _{PK}	71	71	60	57	57	57
	Geometric Mean	481	2.33	6.91	73200	0.0202	4.27
	(CV%)	(33)	(1.00 – 3.50)	(2.88 – 13.6)	(35)	(30)	(24)
Fourth	n _{PK}	31	31	40	27	27	27
	Geometric Mean	556	2.13	8.48	79700	0.0173	4.38
	(CV%)	(17)	(1.00 – 3.00)	(4.19 – 12.7)	(30)	(28)	(17)

AUC, area under the concentration time curve; C_{max}, maximum serum concentration; CL, total body clearance; CV, coefficient of variation; hr, hours; n, number of patients; NSCLC, non-small cell lung cancer; n_{PK}, number of pharmacokinetic observations; PK, pharmacokinetic; t_{max}, time of maximum observed drug concentration; t_{1/2}, terminal elimination half-life; V_{ss}, volume of distribution at steady state.

^a Infusion duration varied from 0.42 to 3.08 hours.

^b Concentration at 0 to 2 hours from end of infusion.

^c Median (min-max) are presented for t_{max}.

^d Geometric mean (min-max) are presented for t_{1/2}.

^e AUC_(0-∞), area under the concentration time curve from time 0 to infinity is presented following first infusion and AUC_(0-tau), area under the concentration time curve during 1 dosing interval (504 hours) is presented following fourth infusion.

^f CL is calculated as dose/AUC_(0-∞) following first infusion and as dose/AUC_(0-tau) following fourth infusion.

Supplemental Table 2. Gene Expression Assays

Target	TaqMan Probes Number	Sequences
IGF-IR	Hs00609566_m1	N/A
INSR (Total IR)	Hs00961554_m1	N/A
INSR (IR-B)	IRB (IR-Long) custom design. cat# AIRR9AF, PN4331348	probe: 5'-TCCCCAGAAAAACCTC-3', F primer: 5'-CCTGCACAACGTGGTTTTCG-3' R primer: 5'-CGGCACCAGTGCCTGAA-3'
IGF-I	Hs01547656_m1	N/A
IGF-II	Hs01005963_m1	N/A
IGFBP3	Hs00181211_m1	N/A
INSIG2	Hs00379223_m1	N/A
ERCC1	Hs01012158_m1	N/A
TYMS	Hs00426586_m1	N/A
IL10	Hs00961622_m1	N/A
ITGB3	Hs01001469_m1	N/A

ERCC1, excision repair cross-complementation group 1; IGF-I, insulin growth factor type I; IGF-II, insulin growth factor type II; IGF-IR, insulin-like growth factor I receptor; IGFBP3, insulin growth factor binding protein-3; IL10, interleukin 10; INSIG2, insulin induced gene 2; INSR (IR-B), insulin receptor B isoform; INSR (Total IR), total insulin receptor; ITGB3, integrin beta-3; N/A, not applicable; TYMS, thymidylate synthase.

Supplemental Table 3. Interaction model: Cox regression of PFS and OS for Total IGF-I and IGFBP-3

Marker	Sample Size	Parameter	High Levels		Low Levels	
			Cixutumumab	Control	Cixutumumab	Control
Total IGF-I (Cutpoint: Q1 = 103 ug/L)	50, 51, 18, 15	mPFS (95% CI)	5.3 (3.5–6.0)	7.1 (5.0–8.7)	5.8 (1.5–8.9)	6.5 (2.1–5.6)
		PFS HR (95% CI)	1.72 (1.07–2.77)		0.60 (0.28–1.31)	
		P value	P = 0.023		P = 0.204	
		Interaction P value	Interaction P = 0.027			
		mOS (95% CI)	NR (8.3–NR)	NR (13.0–NR)	7.5 (2.5–13.0)	5.6 (3.1–6.4)
		OS HR (95% CI)	1.37 (0.70–2.67)		0.73 (0.32–1.63)	
		P value	P = 0.354		P = 0.439	
		Interaction P value	Interaction P = 0.240			
IGFBP-3 (Cutpoint: Q3 = 142.598 nmol/L)	16, 19, 52, 47	mPFS (95% CI)	5.5 (4.1–6.0)	7.9 (7.1–9.7)	4.8 (2.7–6.7)	4.9 (3.9–6.2)
		PFS HR (95% CI)	2.13 (0.94–4.81)		1.10 (0.69–1.74)	
		P value	P = 0.073		P = 0.693	
		Interaction P value	Interaction P = 0.170			
		mOS (95% CI)	9.6 (5.8–NR)	NR (NR–NR)	13.0 (7.5–NR)	8.1 (5.7–NR)
		OS HR (95% CI)	3.07 (0.92–10.25)		0.82 (0.46–1.44)	
		P value	P = 0.057		P = 0.490	
		Interaction P value	Interaction P = 0.045			

Note: Interaction model: Cox regression of PFS/OS includes marker class, treatment, interaction between marker class and treatment, and additional covariates of age group, gender and smoking status. The reported sample sizes represent the number of patients with high (total IGF-I or IGFBP-3) expression in the cixutumumab arm, high (total IGF-I or IGFBP-3) expression in the control arm, low (total IGF-I or IGFBP-3) expression in the cixutumumab arm, and low (total IGF-I or IGFBP-3) expression

in the control arm, respectively. High and low levels were defined as the 75th and 25th percentile cutpoint, respectively. Bolded *P* value indicates statistical significance.

CI, confidence interval; HR, hazard ratio; IGFBP-3, insulin growth factor binding protein 3; IGF-I, insulin growth factor type I; NR, not reported; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; Q1, 1st quartile; Q3, 3rd quartile.

Supplemental Table 4. Interaction model: Cox regression of PFS and OS for ratio of IGF-IR to Total IR (INSR)

Marker	Sample Size	Parameter	High Ratio		Low Ratio	
			Cixutumumab	Control	Cixutumumab	Control
IGF-IR/IR Ratio (Cutpoint: Q3 = 2.49)	11, 16, 42, 39	mPFS (95% CI)	7.0 (3.9–8.9)	2.8 (1.6–6.7)	5.4 (3.1–6.0)	6.2 (4.9–7.9)
		PFS HR (95% CI)	0.61 (0.26–1.43)		1.57 (0.95–2.61)	
		P value	P = 0.249		P = 0.076	
		Interaction P value	Interaction P = 0.057			
		mOS (95% CI)	NR (8.7–NR)	6.1 (4.4–NR)	9.4 (7.3–NR)	11.3 (7.6–NR)
		OS HR (95% CI)	0.46 (0.14–1.53)		1.10 (0.60–2.03)	
		P value	P = 0.189		P = 0.750	
		Interaction P value	Interaction P = 0.193			

Note: Interaction model: Cox regression of PFS/OS includes marker class, treatment, interaction between marker class and treatment, and additional covariates of age group, gender and smoking status. The reported sample sizes represent the number of patients who had a high expression of IGF-IR/IR ratio in the cixutumumab arm, high expression of IGF-IR/IR ratio in the control arm, low expression of IGF-IR/IR ratio in the cixutumumab arm, and low expression of IGF-IR/IR ratio in the control arm, respectively. High and low ratios were defined as the 75th and 25th percentile cutpoint, respectively. CI, confidence interval; HR, hazard ratio; IGF-IR, insulin-like growth factor I receptor; IR, insulin receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; Q3, 3rd quartile.

Supplemental Table 5. Interaction model: Cox regression of PFS and OS for *TP53* and *KRAS* mutations

Marker	Sample Size	Parameter	Mutation Positive		WT	
			Cixutumumab	Control	Cixutumumab	Control
TP53	31, 36, 33, 26	mPFS (95% CI)	5.8 (4.3–7.3)	4.5 (3.9–5.7)	5.8 (2.8–7.4)	7.4 (6.2–10.4)
		PFS HR (95% CI)	0.94 (0.56–1.59)		2.11 (1.11–4.02)	
		P value	P = 0.828		P = 0.020	
		Interaction P value	Interaction P = 0.056			
		mOS (95% CI)	10.6 (8.7–NR)	8.0 (5.9–14.4)	8.9 (7.3–NR)	NR (10.4–NR)
		OS HR (95% CI)	0.68 (0.35–1.32)		1.79 (0.80–4.02)	
		P value	P = 0.255		P = 0.146	
		Interaction P value	Interaction P = 0.067			
KRAS	22, 16, 41, 44	mPFS (95% CI)	4.8 (2.7–7.3)	4.3 (2.7–6.2)	5.8 (4.8–7.4)	6.0 (4.6–7.5)
		PFS HR (95% CI)	0.90 (0.44–1.84)		1.29 (0.79–2.11)	
		P value	P = 0.780		P = 0.310	
		Interaction P value	Interaction P = 0.425			
		mOS (95% CI)	9.4 (5.8–NR)	10.5 (4.2–NR)	13.0 (8.3–NR)	11.3 (7.4–NR)
		OS HR (95% CI)	1.02 (0.44–2.37)		0.95 (0.51–1.77)	
		P value	P = 0.958		P = 0.869	
		Interaction P value	Interaction P = 0.889			

Note: Interaction model: Cox regression of PFS/OS includes mutation status, treatment, interaction between mutation status and treatment, and additional covariates of age group, gender and smoking status. The reported sample sizes represent the number of patients who are mutation positive (*TP53* or *KRAS* gene) in the cixutumumab arm, mutation positive (*TP53* or *KRAS* gene) in the control arm, mutation negative (wild type *TP53* or *KRAS*) in the cixutumumab arm, and mutation negative (wild type *TP53* or *KRAS*) in the control arm, respectively. Bolded *P* value indicates statistical significance.

CI, confidence interval; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; mOS, median overall survival; mPFS, median progression-free survival;

NR, not reported; OS, overall survival; PFS, progression-free survival; *TP53*, tumor protein 53; WT, wild type.

Supplemental Figure 1. Mean (\pm standard deviation [SD]) serum concentration-time profiles on linear scale (left panel) and semi-logarithmic scale (without SD, right panel) of cixutumumab following every 3 weeks of IV infusion of 20 mg/kg cixutumumab over 1.0 to 1.5 hours with cisplatin and pemetrexed as first-line therapy in patients with advanced NSq-NSCLC. Hr, hours.

Supplemental Figure 1. Serum Concentration vs. Time Profile of Cixutumumab